THE IMPORTANCE OF NON-DIABETIC ACIDOSIS.*

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The immense amount of work that has been done upon this very interesting and poorly understood subject since 1877, when Walter first reported acid intoxication in rabbits, gives one some idea of the bearing that it must have on the various processes of health and disease. A careful résumé of the literature is strikingly discouraging, however, because it reveals the fact that many of the features of acid poisoning are as obscure to-day as they were 30 years ago. Whether the condition is essentially a symptom of certain pathological states, whether it is an etiological factor of certain pathological processes, or whether it is simply an associated condition of numerous diseases, are all factors that must be taken into consideration, and yet the diversity of opinion as expressed by different experimenters is such as to overwhelm one in an endeavor to formulate definite conclusions.

Of one point, however, we may be certain and that is that in the large number of conditions in which acidosis is either an etiological factor, a symptom or a pathological result, we may by combating the acidosis improve the patient's condition. As clinicians, that is a factor which must constantly be taken into consideration.

The object of this paper is not to draw attention to any new data upon this much complicated subject, but rather by reporting a number of interesting cases in which acidosis was a prominent feature, to recall the fact that acetonuria and diaceturia are far more frequent than those urinary conditions for which we habitually test, and when present are unquestionably responsible for, or at least represent a part of, a distinct toxic process. Although this paper is essentially a clinical one, it may be well to at least call attention briefly to the experimental facts that we have at our disposal from which conclusions can be drawn.

Ewing, in the Transactions of the Association of American Physicians, 1908, calls attention to two experimental prototypes of acidosis. First, the toxemia resulting from the ingestion of HCl, first described by Walter; and second, the toxemia resulting from liver extirpation, or following an Eck's fistula, first described by Minkowski. Animals subjected to these two experiments show definite pathological and chemical differences. Those dogs suffering from HCl poisoning show no prominent post-mortem changes. The urine shows a marked excess of acetone compound. The ammonia is proportional to these acids and the amino acid nitrogen is slightly increased. The clinical types of acidosis comparable to HCl poisoning in animals are diabetes, with which this article does not deal, Kussmaul's coma, starvation and febrile acid intoxication. Animals with Eck's fistulæ or whose livers have been extirpated, show on the contrary excessive fatty degenerative processes. The urine contains an excess of lactic acid, glucose is often present; the acetone products are secondary, ammonia is present in excess of the fatty acids and the amino acid nitrogen is much increased. Allied to these clinically, we have cases of phosphorus poisoning, pernicious vomiting of pregnancy, acute yellow atrophy of the liver, eclampsia, delayed chloroform poisoning and cyclic vomiting.

It is at least interesting to note the difference in origin of the high ammonia content in the two groups of cases. In the first, the high ammonia represents an effort to neutralize the acid products. In the second group of cases, it is due to improper formation of urea incidental to the marked destruction of liver tissue.

Up to 1905 most of the theories concerning the formation of acid products were purely problematical, and since that time, largely through the work in Knoop's laboratory, some of the more obscure points have been elucidated although the question of the toxicity is still a much disputed one. In the early eighties Gerhardt discovered the Fe Cl_2 reaction in diabetic urine, and about the same time the younger Von Jaksch isolated diacetic acid, which he found responsible for this reaction and to which he ascribed all the symptoms of acid poisoning. Stadelmann in 1883, in an effort to understand the high ammonia content in diabetes, discovered Beta oxybutyric acid.

As a result of the investigative work done by Knoop in 1905, a great deal was added to our knowledge of the formation of the acid products. Before that time it had been definitely conceded that the acetone bodies might be formed from either proteins or fats, but the process had never been observed. Geelmuyden had demonstrated that the addition of large amounts of fat increased acetonuria. Rosenfeld showed that the acid products appeared in the urine in carbohydrate free diets. Hirschfeld and Geelmuyden, experimenting on carbohydrate administration in the acidosis of starvation, had concluded that from 50—100 gms. of carbohydrate served to abolish the acetonuria. It remained, as has been stated, for Knoop to demonstrate the formation of the acetone products from the fatty acids. Under normal conditions the aromatic acids are destroyed so quickly in the body that the steps can not be followed. By adding the Benzen radicle C_6H_5 to the fatty acids, Knoop retarded oxidation and was able to show the formation of the acetone bodies. Embden passed aerated blood through excised livers and was able to demonstrate the presence of a small quantity of acetone in the blood. He added certain organic acids to the aerated blood on repeating the same experiment and was able to increase the formation of acetone. Working in the same laboratory, Baer and Blum fed these same aromatic acids to diabetic cases and were able to increase the acetonuria. Having demonstrated that fat ingestion through the action of aromatic acids is responsible in certain pathological conditions for the development of acid intoxication, it is perfectly rational to assume that proteins through their amino acids have some part in the same

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process. The amino acids have only to lose the NH_2 group to revert to fatty acid and as such act in the same manner as the acid radicles derived from fat tissues. Folin of Boston, before the Association of American Physicians, 1907, in discussing the acid intoxication theory, asks the following questions:

1. "Why does the oxidation of carbohydrates diminish the formation of acid products?

2. Why are oxybutyric and diacetic acids formed rather than lactic and oxalic acids?

3. Is the universal assumption that oxybutyric acid is the forerunner of diacetic acid and acetone a correct one?"

To these questions may be added:

4. Are acetone and diacetic acid ever present in quantities sufficiently large to produce toxic symptoms *per se?*

5. If not, are they responsible for the toxemia by their action on the pathological processes?

6. What bearing upon acid intoxication has alkali absorption from the tissues?

In short, in discussing acidosis one is overwhelmed by a large number of unsolved problems; and there is no field in experimental medicine today so fertile as that which deals with acid intoxication, its causes, its effects, and its meaning. Edsall, in a discussion of acidosis in the *British Medical Journal,* touches on some of these points. He states the usual theory that acetone and diacetic acid are derivatives of Beta oxybutyric acid, but that, on the other hand, it must be a reversible process because by feeding animals diacetic acid, Beta oxybutyric acid is found in the urine. He further states that acetone and diacetic acid are never present in amounts sufficient to be toxic, but that these favor autolysis and that the grave symptoms often accompanying their presence may be due to their autolytic action.

A great deal of time might be given to further portrayal of the subject under discussion from the theoretical and experimental side, but unfortunately this would not enable us to draw any definite conclusions as to even a problematically correct understanding of it. We know only that this toxemia is associated with a great many pathological states and that it is a clinical entity which must be combated, if not for the toxic effects that the acid products themselves have, at least for the very serious symptoms which are so frequently associated with them.

Most authors and most text-books give a detailed classification of the diseases with which acidosis is most often associated, and to make a paper complete this is unquestionably reasonable. It hardly seems exaggeration, however, to state emphatically that there is scarcely a pathological condition to which humans are heir, with which there may not be associated at times a severe degree of acid intoxication. Whether it be to the internist, the surgeon, the pedriatrist, the obstetrician, the aurist, or oculist, patients will constantly present themselves with obscure symptoms, the origin of which either primarily or secondarily is an acid poisoning. The following conditions are generally recognized, however, as most frequently giving rise to acidosis:

1. *Starvation.* There is probably no single condition that is more frequently responsible for the presence of acid products in the urine than actual starvation, either through restriction of diet or through lack of ability to assimilate the food that is given.

2. *Gastro-intestinal Diseases.*

3. *Specific Infections,* Diphtheria, Pneumonia, etc.

4. *Diabetes.*

5. *Cachexia* from Malignant Disease.

6. *Poisons.* Phosphorus, Morphine, Sodium, Salicylates, Phloridzin.

7. *Anesthetics.*

8. *Acute Yellow Atrophy of Liver.*

9. *Toxemia of Pregnancy,* Eclampsia.

10. *Recurrent or Cyclic Vomiting of Childhood.*

11. *Ingestion of Large Quantities of Fat.*

It is truly surprising with the very great simplicity attached to the qualitative tests for diacetic acid and acetone that so many urinalyses are done without any attention being paid to their presence. Both tests are far more simple than the Fehling or allied reactions for sugar, they are found positive a thousand times more frequently than the sugar test, and yet, surprising as it may seem, many laboratory experts neglect them. There is no more striking reaction in chemical pathology than the port wine red color which is developed when tincture of the chloride of iron is added to a urine containing diacetic acid; and the test for acetone by adding sodium hydrate and iodine to the urine and gently beating, is surely a simple one, for we are all acquainted with the odor of iodoform, which is developed along with the presence of iodoform crystals if the amount of acetone is considerable.

T. S. Hart of New York, in the *Archives of Internal Medicine,* 1911, describes a simple quantitative method of determining the amount of diacetic acid. He has two standard solutions: I, contains ethyl acetate 1.0, alcohol 25., water 1000.0; II, contains $Fe\,Cl_2$ 100, H_2O 100. To 10 cc. of I he adds 1 cc. of II and to 10 cc. of urine he adds 1 cc. of II. He dilutes the urine sufficiently to make the color the same as that obtained with the standard solutions and the amount of dilution necessary determines the index. His conclusions are as follows:

I. Acidosis index is a measure of the acidosis based on the depth of color obtained with the $Fe\,Cl_2$ reaction.

II. The values thus obtained run parallel with a polariscopic method, to ammonia output and chemical determinations.

III. The method is probably better than the polariscopic method, basing his conclusion on Magnus-Levy's statement that polariscopic values are exaggerated.

IV. The method is better than ammonia determinations, especially if alkalies are being given.

V. It is simple.

It is of course very questionable whether quantitative tests are essential in the determination of degree of acidosis. After all, the problem deals with so many uncertainties that the results obtained by quantitative reactions are by no means always an indication of the clinical condition. One sees constantly cases in which the amount of diacetic acid and acetone is very small and yet the symptoms very marked, and the reverse is likewise frequently encountered.

Very little mention has been made in this paper of Beta oxybutyric acid, not because the importance of this toxic substance is not thoroughly appreciated but because the tests for it are so complicated as to render them almost impossible for the clinician to perform.

Without further elaboration on the causes and results of acid intoxication, the following reports of a number of interesting and obscure cases will graphically show the very important role that acidosis plays in disease:

I. Diagnosis: Colitis and acidosis. Mrs. A., age 54, was first seen in February, 1911, suffering from a typical attack of mucous colitis. Except for a marked indicanuria at that time the urinalysis was negative. She was put under treatment and her symptoms rapidly improved. Two weeks later she was taken acutely ill with general aches and pains, and of her own accord took 15 grains of aspirin. The following morning she developed a fine papular erythematous rash over her whole body. Her temperature was normal. Throat and tongue negative. From the appearance of the rash it might have been either a toxic erythema of drug or intestinal origin or German measles. The rash persisted four days and with its disappearance patient developed a very severe frontal headache. This persisted and with it the blood pressure rose to 180 systolic. Coincidental with the rise in blood pressure, patient complained of a peculiar disturbance in sight which she described as a sensation of wheels turning around and around. This syndrome immediately suggested a kidney complication, and a urinalysis showed a trace of albumen and some granular casts. More as a matter of routine than otherwise, acetone and diacetic acid were tested for and both were present in excessively large amounts. Patient was immediately put upon enemas of glucose and bicarbonate of soda, 4% and 3% respectively. Bicarbonate of soda in 10 grain doses was given every 2 hours, and a full carbohydrate diet prescribed. At the end of one week patient's general condition was much improved. Headaches had greatly ameliorated and the eye condition was less marked. An examination of the eye showed no tendency to glaucoma, of which the symptoms were suggestive, but a marked injection of the choroidal vessel. For two months subsequently patient had occasional return of the headache and eye symptoms coincidental to reappearances of the diacetic acid and acetone in the urine, but they rapidly disappeared under treatment.

II. Diagnosis: Phlebitis of femoral vein. Acidosis. J. R. B., age 10 years, was taken suddenly ill March 25th, 1911, with excruciating pain in the right thigh and leg. The exact location of the pain could not be defined. With the appearance of the pain there developed slight rise in temperature and loss of appetite. Questioning revealed the fact that patient had suffered with a similar attack 5 weeks before for which he had been confined to his bed for 7 days. Physical examination was negative as far as the thorax and abdomen were concerned. The right lower extremity was swollen in its entirety but there was no edema into the subcutaneous tissues. On measurement, the circumference of the right thigh was 2 cm. greater than left thigh and the right leg was 1½ cm. greater in circumference than left leg. Over the course of the femoral vein there was tenderness. Motion was limited in every direction by the excruciating pain that patient suffered. The extremity seemed at greatest ease when patient was in erect position and leg was hanging. Spine was normal. X-ray picture of hip joint and thigh negative. Leukocyte count 12,000. Differential count negative. Urinalysis negative except for excess of acetone and diacetic acid. It was learned that patient had been eating meat three times a day and that bowel movements for some time had been very foul in odor. Under treatment, which consisted of carbohydrate diet, glucose frequently during the day in the form of Karo syrup, sodium bicarbonate grains x q 2 H, symptoms subsided entirely in eight days.

III. Diagnosis; Nephritis and acidosis. Mrs. R. S. Age 42. Family and previous history negative. The duration of present condition is rather indefinite. The chief symptoms are headache, dizziness, edema of lower extremities, dyspnea on exertion and disturbance in vision. The history is not at all satisfactory as patient has no idea of duration of illness.

The physical examination revealed a very obese woman of 42. Heart. Percussion absolutely unsatisfactory on account of thickness of thoracic wall, but definite hypertrophy unquestionably present. No murmurs. Marked accentuation of second aortic. Abdomen. No ascites. Liver extends two fingers below free border of ribs. Decided edema of lower extremities. Blood pressure, systolic 180. Retinal examination shows a hemorrhagic retinitis. Urinalysis: sp. grav. 1026. Albumen .05%. Sugar negative. Microscopical examination shows many hyaline and granular casts. A very large amount of acetone and diacetic acid is present.

Patient was put to bed and placed upon large doses of alkali and glucose. With the disappearance of her acidosis her symptoms greatly improved, despite the severe degree of nephritis.

IV. Diagnosis: Septicemia and acidosis. B. D., 14 years. Family and previous history negative. One week before patient was seen she was suddenly taken ill with malaise, headache, and high temperature. These symptoms had persisted, the temperature being 104° in the morning and normal at night. There had been no chill or septic sweating. For 24 hours patient had complained of tenderness along the anterior cervical glands on the right side. There had been no other local symptoms referable to any other organ in the body.

Physical examination was negative with the exception of the hypertrophied and tender cervical glands and some congestion in the throat. Urinalysis was negative except for intense acidosis. W. B. C. 14,000. Polymorphonuclears 94%. In view of the septic temperature, even though inverse in character, the polymorphonuclear relative leukocytosis, and the tenderness over the cervical glands on the right side, a diagnosis was made of septicemia emanating from the throat. Blood culture was not done.

Treatment. On account of the intense acidosis brought on probably both by the high temperature and limited diet, alkalies were administered and carbohydrates given in large amounts. The symptoms subsided in a few days.

V. Diagnosis: Toxemia of pregnancy. Mrs. W. F., 34 years. Family and previous history have no bearing. Present illness began 7 days before patient was seen, in the eighth month of an apparently normal pregnancy, with backache and nausea,

which symptoms persisted 24 hours but ameliorated on the administration of cathartics. Forty-eight hours later the symptoms became very much worse and intense headache was added to the marked vomiting and backache. At the same time decided tenderness appeared in the right hypochondrium and patient developed slight temperature, 99°-100°.

Physical examination shows very well developed, well nourished woman of about 35 years. Cheeks flushed. Expression very apathetic. Atmosphere of room is permeated with an aromatic odor that suggests acetone and diacetic acid. This is particularly marked in the breath. Glands negative. Throat negative. Heart and lungs normal. Abdomen distended by eight months' pregnant uterus. Liver dulness begins at 5th rib and extends 2 finger's-breadth below free border of ribs. There is a very definite tenderness over the border of the liver. Fetal heart sounds audible and of good quality. Pulse 110. Temperature 101°.

Urine. Brownish amber, cloudy, acid, 1020, albumen 0.1%, sugar negative. Acid products, acetone and diacetic acid in great excess. Indican great excess. Microscopical examination showed many granular casts.

It seemed wise to temporize 24 hours, and patient was put upon full doses of alkalies and carbohydrates. At the end of 24 hours toxemia was greater, icterus had developed, all of the pre-existing symptoms were more marked, and it was deemed advisable to induce labor, which was done by Dr. Wakefield at 11 p. m. The alkaline treatment was continued. Patient went into labor at 5 a. m. and was delivered 8½ hours later. One of the most striking facts noted in connection with this case is that the acid products had disappeared from the urine within 18 hours of the time of delivery. Recovery was uneventful. This same patient has within the past month undergone a major operation. Within a few hours of the administration of the anesthetic she developed an intense acidosis from which she recovered relatively very slowly. It is interesting as suggesting the question of individual predisposition to acidosis.

VI. Diagnosis. Cyclic Vomiting of Childhood. G. Y., 6 Years. Family history has no bearing. Previous history: For three years patient has had spondylitis deformans. Up to 3 weeks ago patient had been for one year confined to her bed. Present illness began in May, 1911, with the occurrence of a very severe attack of persistent vomiting, which lasted several days. Since that time patient has had these attacks every month with one or two exceptions. Attacks can usually be foretold by loss of appetite, coated tongue, and a very bad odor to the breath. Temperature rises during the attack to about 101°, and there is some tenderness in the right iliac region. One very peculiar feature of these attacks is that at the end of them patient has a hematuria. There is no headache.

Physical examination at this time, which was between attacks, was negative except for the presence of a very marked deformity due to a tubercular spondylitis. Urinalysis was absolutely negative.

Treatment at this time was not instituted. Mother was furnished with Tr. ferri chloride and test tube and instructed how to test the urine every morning for diacetic acid, which test up to the onset of next attack of vomiting, two weeks later, was quite negative. Two weeks after the patient was seen, mother first noted the premonitory symptoms of an attack, and on the following morning patient began to vomit. The first specimen of urine that morning did not show any acid product, but the second urine voided 4 hours later contained a large amount of diacetic acid, which the mother detected, and acetone was also present.

Treatment. Patient was immediately put upon 4 hour enemas containing 60 grains of bicarbonate of soda in 4% sugar solution, and the enema was held one hour and in that way retained. Vomiting ceased at the end of 24 hours and milk of magnesia was immediately started by mouth, one drachm every hour until one ounce had been given. Glucose in the form of Karo syrup was given in large quantity with carbohydrates and sodium bicarbonate gr. x every two hours. The enemata were discontinued and patient rapidly recovered.

The diagnosis having been made, an effort was then made to prevent the attacks. Bicarbonate of soda gr. v, 3 times a day was continued, and patient put upon an easily assimilable diet. Mother was instructed on the appearance of premonitory symptoms to administer milk of magnesia one drachm every hour for eight doses, and increase the bicarbonate soda to 10 grs. every two hours, and to use glucose freely by mouth. Since these directions have been followed, three attacks have been aborted and the acidosis has not developed.

One might go on indefinitely reciting cases in which a profound degree of acidosis was a marked feature. A careful review of these cases can lead to but one conclusion, and that is either as a cause or result of many pathological conditions we have an abnormal metabolism characterized by imperfect oxidation and the presence of abnormal acid products in the urine. The subject is still so thoroughly in the experimental stage that one is not able to state exactly why acidosis is so frequently present. Likewise, one is confused to note that acidosis may be fairly marked and the symptoms relatively slight. A hundred unanswered and unanswerable questions might occur to everyone, but of one fact we may be definitely certain, and that is that either independently, or as a complication of other diseases, we have in medicine a condition of acid intoxication which either *per se* or indirectly is responsible for definite symptom complexes, and that it is the duty of every one of us to be on the alert for the development of this condition because, more than can be said for many medical disturbances, it can be absolutely relieved by appropriate treatment.

TRANSFUSION.*

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Although in the broader sense, transfusion includes the introduction of any fluid into the body, even saline solutions, we will use the word only to mean the causing of flow of blood directly from the vessels of one human being into the blood vessels of another.

The ten minutes allotted me is so short I will omit reference to the history of transfusion, and will confine my remarks chiefly to the technic and briefly to the indications, contraindications and the citation of a few cases.

Of the various methods the first I wish to mention is that of the direct anastomosis of the radial artery of the donor with a superficial vein (usually the median basilic) of the recipient. This is known as Carel's method and is described in the *Bulletin of Johns Hopkins Hospital,* 1907, and very excellently described and illustrated by Crile in his book on "Hemorrhage and Transfusion," published in

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